



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2012-N-1029]

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; General Licensing Provisions; Section 351(k) Biosimilar Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that a proposed collection of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

DATES: Fax written comments on the collection of information by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202-395-7285, or emailed to oir_submission@omb.eop.gov. All comments should be identified with the OMB control number 0910-New and title "General Licensing Provisions; Section 351(k) Biosimilar Applications". Also include the FDA docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION: In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

General Licensing Provisions; Section 351(k) Biosimilar Applications--(OMB Control Number 0910-New)

On March 23, 2010, the President signed into law the Patient Protection and Affordable Care Act (Affordable Care Act) (Public Law 111-148). The Affordable Care Act contains a subtitle called the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) which amends the Public Health Service Act (PHS Act) and establishes an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product. (See sections 7001 through 7003 of the Affordable Care Act.)

Section 351(k) of the PHS Act (42 U.S.C. 262(k)), added by the BPCI Act, sets forth the requirements for an application for a proposed biosimilar product and an application or a supplement for a proposed interchangeable product. Section 351(k) defines biosimilarity to mean “that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful

differences between the biological product and the reference product in terms of the safety, purity, and potency of the product”. (See section 351(i)(2) of the PHS Act.) A 351(k) application must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and clinical studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application. (See section 351(k)(2) of the PHS Act.) To demonstrate interchangeability, an applicant must provide sufficient information to demonstrate biosimilarity and that the biosimilar biological product can be expected to produce the same clinical result as the reference product in any given patient and, if the biosimilar biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biosimilar biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch. (See section 351(k)(4) of the PHS Act.) Interchangeable products may be substituted for the reference product without the intervention of the prescribing health care provider. (See section 351(i)(3) of the PHS Act.) This Federal Register information collection document begins the process of requesting public comment and obtaining OMB approval for the information collection regarding the burden on the submission of a 351(k) application not otherwise covered by existing OMB approvals.

In estimating the information collection burden for 351(k) applications, FDA has reviewed the collection of information regarding the general licensing provisions for biologics license applications under section 351(a) of the PHS Act to OMB (approved under OMB control number 0910-0338). For the information collection burden for 351(a) applications, FDA described § 601.2(a) (21 CFR 601.2(a)) as requiring a manufacturer of a biological product to

submit an application on forms prescribed for such purpose with accompanying data and information including certain labeling information to FDA for approval to market a product in interstate commerce. FDA also added in the burden estimate the container and package labeling requirements provided under §§ 610.60 through 610.65 (21 CFR 610.60 through 610.65). The estimated hours per response for § 601.2, and §§ 610.60 through 610.65, were 860 hours.

In addition, in submitting a 351(a) application, an applicant completes the Form FDA 356h “Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use.” The application form serves primarily as a checklist for firms to gather and submit certain information to FDA. The checklist helps to ensure that the application is complete and contains all the necessary information, so that delays due to lack of information may be eliminated. The form provides key information to FDA for efficient handling and distribution to the appropriate staff for review. The estimated burden hours for biological product submissions using FDA Form 356h are included under the applicable requirements approved under OMB control number 0910-0338.

FDA intends for an applicant to submit a 351(k) application following Form FDA 356h, modifying the information submitted to support the information required under section 351(k) of the BPCI Act. To submit an application seeking licensure of a proposed biosimilar product under section 351(k)(2)(A)(i) and (k)(2)(A)(iii), FDA believes that the estimated burden hours would be approximately the same as noted under OMB control number 0910-0338 for a 351(a) application--860 hours. The burden estimates for seeking licensure of a proposed biosimilar product that meets the standards for interchangeability under section 351(k)(2)(B) and (k)(4) would also be 860 hours. Until we gain more experience with biosimilar applications, FDA believes this estimate is appropriate for 351(k) applications because to determine biosimilarity or

interchangeability of a proposed 351(k) product, the application and the information submitted is expected to be comparably complex and technically demanding as a proposed 351(a) application. FDA may determine, in its discretion, that an element required under a 351(k) application to be unnecessary to support licensure of a biosimilar or interchangeable product. In those cases, the number of hours per response may be less than the hours estimated.

A summary of the collection of information requirements in the submission of a 351(k) application as described under the BPCI Act follows:

Section 351(k)(2)(A)(i) requires manufactures of 351(k) products to submit an application for FDA review and licensure before marketing a biosimilar product. An application submitted under this section shall include information demonstrating that:

- The biological product is biosimilar to a reference product based upon data derived from analytical studies, animal studies (including toxicity) and a clinical study or studies (including immunogenicity and pharmacokinetics or pharmacodynamics). The Secretary of Health and Human Services (the Secretary) may determine that any of these elements is unnecessary.
- The biological product and reference product utilize the same mechanism or mechanisms of action for the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling, but only to the extent the mechanism or mechanisms of action are known for the reference product.
- The condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product.

- The route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product.
- The facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent.

Section 351(k)(2)(A)(iii) requires the application to include publicly-available information regarding the Secretary's previous determination that the reference product is safe, pure, and potent. The application may include any additional information in support of the application, including publicly-available information with respect to the reference product or another biological product.

Under section 351(k)(2)(B) and (k)(4), a manufacturer may include information demonstrating that the biological product meets the standards for interchangeability either in the application described in this document to show biosimilarity, or in a supplement to such an application. The information submitted to meet the standard for interchangeability must show that: (1) The biological product is biosimilar to the reference product and can be expected to produce the same clinical result as the reference product in any given patient and (2) for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.

In addition to the collection of information regarding the submission of a 351(k) application for a proposed biosimilar or interchangeable biological product, section 351(l) of the BPCI Act establishes procedures for identifying and resolving patent disputes involving

applications submitted under section 351(k) of the PHS Act. The burden estimates for the patent provisions under section 351(l)(6)(C) of the BPCI Act are included in table 1 of this document and are based on the estimated number of 351(k) biosimilar respondents. Based on similar reporting requirements, FDA estimates this notification will take 2 hours. A summary of the collection of information requirements under 351(l)(6)(C) follows:

Not later than 30 days after a complaint from the reference product sponsor is served to a 351(k) applicant in an action for patent infringement described under 351(l)(6), section 351(l)(6)(C) requires that the 351(k) applicant provide the Secretary with notice and a copy of such complaint. The Secretary shall publish in the Federal Register notice any complaint received under 351(l)(6)(C)(i).

FDA has not received any 351(k) applications to date. Under table 1 of this document, the estimated number of respondents submitting 351(k) applications is based on the estimated annual number of manufacturers that would submit the required information to FDA and the estimated annual number of 351(k) submissions FDA would receive. In making this estimate, FDA has taken into account, among other things, the expiration dates of patents that relate to potential reference products, and general market interest in biological products that could be candidates for 351(k) applications.

On November 2 and 3, 2010, FDA held a public hearing and established a public docket to obtain input on specific issues and challenges associated with the implementation of the BPCI Act. (See Docket No. FDA-2010-N-0477.) Based in part on this input, FDA announced the availability of three draft guidances describing FDA's current interpretation of certain statutory requirements added by the BPCI Act as well as quality and analytical issues, demonstrating biosimilarity, and implementation policy issues. These draft guidances are: "Biosimilars:

Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009,” “Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product,” and “Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.” The Federal Register documents for these guidances reference this Federal Register information collection document regarding the burden on the submission of a 351(k) application not otherwise covered by existing OMB approvals. In addition, we note that the draft guidance on “Scientific Considerations in Demonstrating Biosimilarity to a Reference Product” recommends that labeling for a product subject to approval under section 351(k) include statements that indicate that: (1) The product is approved as biosimilar to a reference product for stated indication(s) and (2) the product (has or has not) been determined to be interchangeable with the reference product. FDA has determined, under 5 CFR 1320.3(c)(2)), that these labeling recommendations are not “collections of information” for the purposes of the PRA because the statements will comprise solely information that FDA will supply to the applicant for the purpose of disclosing it to the public, i.e. FDA’s determination upon review of the application submitted under section 351(k), that the product is biosimilar and/or interchangeable to its reference product.

In the Federal Register of February 15, 2012 (77 FR 8880), FDA published a 60-day notice requesting comments on the information collection for the requirements for an application for a proposed biosimilar product and an application or a supplement for a proposed interchangeable product. In the Federal Register of February 23, 2012 (77 FR 10752), FDA published a correction to the 60-day notice providing the correct docket number to submit comments. FDA received no comments that pertained to the information collection analysis.

FDA estimates the burden of this collection of information as follows:

Table 1.--Estimated Annual Reporting Burden¹

351(k) Application for Biosimilars (42 U.S.C. 262(k))	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
351(k)(2)(A)(i) and (k)(2)(A)(iii)	2	1	2	860	1720
351(k)(2)(B) and (k)(4)	1	1	1	860	860
351(l)(6)(C)	2	1	2	2	4

¹There are no capital costs or operating and maintenance costs associated with this collection of information.

Dated: May 17, 2012.

Leslie Kux,

Assistant Commissioner for Policy.

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